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Altered Resting State Functional Connectivity of Anterior Cingulate Cortex and Executive Dysfunction in Obsessive-Compulsive Disorder

강박증에서 앞쪽 띠피질을 중심으로 한 휴지기 기능적 뇌연결성의 변화와 집행기능 저하

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윤 제 연

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Altered Resting State Functional Connectivity of Anterior Cingulate Cortex and Executive Dysfunction in Obsessive-Compulsive Disorder

By

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A thesis submitted in partial fulfillment of the requirement for the Degree of Master of Philosophy in medicine (Department of Psychiatry) at Seoul National University College of Medicine

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ABSTRACT

Introduction: The anterior cingulate cortex (ACC) is one of the prefrontal targets of the cortico-striato-thalamo-cortical (CSTC) loops in obsessive-compulsive disorder (OCD) and has been regarded as a neural correlate of executive dysfunction. We investigated the resting state functional connectivity networks (rs-FCNs) of ACC functional subdivisions with the aim of clarifying the relationship between rs-FCN derangements and executive dysfunction in patients with OCD

Methods: Twenty-one patients with OCD were recruited from Seoul National University Hospital and 22 healthy volunteers (HC) underwent a resting state functional magnetic resonance imaging (fMRI) scan. The rs-FCN maps were depicted using five region-of-interest (ROI) seed regions systemically placed throughout the ACC. Correlations between the five neuropsychological test performances and the regional ACC seed-based rs-FCNs with significantly altered functional connectivity strength were examined in between-group analyses.

Results: The rs-FCNs showed rostral/caudal functional distinction in both groups. Between-group analyses revealed significantly weaker functional connectivity of the OCD group in the claustrum, thalamus, and inferior parietal lobule (IPL). Stronger rs-FC between ACC Seed S5 and the right claustrum correlated with higher Rey–Osterrieth Complex Figure Test organization scores. The prolonged Trail Making Test part-A reaction time demonstrated a correlation with weaker rs-FC strength between ACC Seed S7 and the right IPL.

Conclusion: Altered strengths in the functional connectivity between ACC seeds versus specific brain areas of the CSTC loop may be the neural correlates of executive dysfunction in OCD. Additionally, the inferior parietal lobule could be one of the important brain regions included in the OCD pathophysiologic loops.

Keywords: Anterior cingulate cortex, resting state functional connectivity, functional magnetic resonance imaging, obsessive-compulsive disorder, executive dysfunction

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LIST OF ABBREVIATIONS

ACC: anterior cingulate cortex

BA: Brodmann area

BAI: Beck Anxiety Inventory

BDI: Beck Depression Inventory

COWAT: Controlled Oral Word Association Test

CSTC: cortico-striato-thalamo-cortical

DLPFC: dorsolateral prefrontal cortex

DMN: default mode network

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition

ERN: error-related negativity

fMRI: functional magnetic resonance imaging

IPL: inferior parietal lobule

IQ: intelligence quotient

K-WAIS: Korean-Wechsler Adult Intelligence Scale

MNI: Montreal Neurologic Institute

OCD: Obsessive-compulsive disorder

OFC: orbitofrontal cortex

RCFT: Rey-Osterrieth Complex Figure Test

RS-FCN: resting state functional connectivity network

ROI: Region of Interest

PCC: posterior cingulated cortex

SCID-IV: Structured Clinical Interview for DSM-IV

SCID-NP: Structured Clinical Interview for DSM-IV Non-patient Edition

SCWT: Stroop Color-Word Test

SPM: Statistical Parametric Mapping

TMT: Trail Making Test

WCST: Wisconsin Card Sorting Test

Y-BOCS: Yale-Brown Obsessive Compulsive Scale

INTRODUCTION

Obsessive–compulsive disorder (OCD) is a relatively common and chronically disabling neuropsychiatric disorder with an average lifetime prevalence of 2%–3% (1). The OCD is characterized by intrusive thoughts which the patient attempts to neutralize by either mental or motoric compulsive acts (2). And the typical themes of these intrusive thoughts occurring in OCD relate to contamination fear, symmetry, aggression, sexuality and religious ides (3). Cognitive behavioral models of OCD pathophysiology posit dysfunctional inhibitory control system during symptom provocation paradigms and neuropsychological tests requiring executive control of motor inhibition and cognitive flexibility (4).

Taking heterogeneous symptomatology of the OCD into consideration, more common disease characteristics encompassing diverse OC symptom dimensions are needed. Endophenotypes are measurable disease-associated traits which could occur even during the subclinical disease status and have a simpler relationship with underlying genes than clinical measurements, assisting in the identification of genes that result in vulnerability to the disorder (5). From this perspective, neurocognitive dysfunctions are considered among the most promising candidates for endophenotypes in many psychiatric disorders including OCD (6), in which executive dysfunctions in the domains of nonverbal memory (7), cognitive flexibility (8) and response inhibition are among the most frequently replicated findings. Executive dysfunctions may qualify as a suitable endophenotype candidate for OCD. Concordance rates in neuropsychological task performance suggest that decision-making and planning deficits aggregate in these families and therefore might be a heritable component of OCD (9).

The neuro-anatomical model of obsessive-compulsive disorder (OCD) proposes that the clinical symptoms and related cognitive deficits of OCD are caused by dysfunctional cortico–striato–thalamo-cortical (CSTC) loops. The CSTC loops are composed of several parallel running loops encompassing prefrontal areas of the orbitofrontal cortex (OFC), the anterior cingulate gyrus (ACC), the striatum including caudate nucleus and thalamus (10). Dysfunctional CSTC loops could result in primary executive dysfunction, which may affect secondary nonverbal memory function by way of impaired information processing strategies (11). And performances of the Rey–Osterrieth Complex Figure Test (RCFT) – a neuropsychological test assessing visuospatial constructional ability, visual memory, and executive function of visual organizational strategies (12) - and the Trail Making Test (TMT) – a neuropsychological test measuring attention, visuospatial working memory and executive function of the set-shifting (13) – are shown to be significantly impaired in OCD patients(13). But the exact neural correlates of these neuropsychological impairments have not been investigated in OCD yet.

As an integrative center of several cognitive-behavioral, emotional-autonomic and motor neural networks (14, 15), the anterior cingulate cortex (ACC), one of the prefrontal targets of the CBTC loops, has been suggested as a putative neural correlate of executive dysfunction in OCD. ACC is anatomically, metabolically and functionally altered in OCD. ACC is linked to difficulties with set-shifting (16), decision making and both action (17) and error-monitoring (18, 19) in OCD patients. Previous structural neuroimaging studies have revealed some structural alterations in ACC morphology - namely, reduced grey matter (GM) volume of the left ACC (20), left caudal ACC (21) and bilateral dorsal ACC (22) – in the OCD patients, when compared to the healthy control (HC) group. ACC-associated white matter (WM) alterations were also reported, as white matter (WM) volume (23) and fractional anisotropy (24) of the left ACC were significantly reduced in the OCD group.

Not only these structural changes, in OCD patients, ventral frontal-striatal areas such as OFC, caudate head, insula and ACC are hyper-activated during symptom provocation (25) or during resting states (26). And in several task-based fMRI studies, dysfuctional ACC activation in OCD has been linked to the executive dysfunction of set-shifting(16), action monitoring (17), error-processing (18) and cognitive control of emotion (27). Also, in a recent clinical study using Tower of London test as a task, as task load increases, pediatric drug-naïve OCD patients showed more recruitment of ventro-lateral and medial prefrontal cortex and insula and ACC when compared to HC group, which were normalized after cognitive behavioral treatment (CBT) sessions (28). Using EEG source localization method, hyperactive error-related negativities (ERNs), which is related to the obsessive thoughts and compulsive acts of OCD patients and is thought to reflect the activities of a hyperactive cortico-striatal circuit during action monitoring, was detected in the rostral ACC of OCD patients with severe OC symptomatology (29). Likewise, previous ^{1}H-magnetic resonance spectroscopy (MRS) studies have reported reduced N-acetyl-aspartate (NAA) level and glutamate-glutamine level in the ACC of OCD patients (30, 31). All these anatomical and metabolic alterations and changes in anatomical connectivity between ACC and other brain area are reflected in brain studies using EEG and functional magnetic resonance imaging (fMRI). In an EEG study for severe OCD patients, error-related negativities (ERNs) were localized to the rostral ACC (29). (32, 33). But to overcome the limitations of previous task-based fMRI studies, in which the exact loci and extents of ACC activation became diverse depending upon the function explored and the task employed (34), another functional neuroimaging approach which could demonstrate the pattern of ACC functioning in wider dimension of .cognitive function has been required.

As both cognitive functioning and OC symptomatology are manifested over the integrated activity of multiple brain regions, investigating the coupling between several brain regions could be more useful to understand complex brain functioning. These relationships between brain regions can be measured under the notion of ‘functional connectivity’, the spatiotemporal correlations between spatially distinct brain regions (35) And among the functional connectivites, the resting-state functional connectivity networks (rs-FCNs), spontaneous low-frequency fluctuations (0.01–0.08 Hz) of resting-state blood oxygenation level-dependent signal, have been widely used to characterize the intrinsic or spontaneous neuronal activity of the normal subjects as well as the psychiatric or neurologic patient groups (36). The rs-FCN approach could reveal the degree of functional-metabolic coherence between brain regions during task-free status (37), in which diverse rs-FCNs including the default mode network (DMN) – related to internally oriented cognition and deactivated when required to act goal-directed behavior (38), the dorsal attention network (39), the somatosensory network (40) and the paralimbic network(41) coexist along the whole brain area.

The ACC, composed of cyto-architectonically (42) and functionally (14) heterogeneous sub-regions, works as the integrative centers for several cognitive–behavioral, emotional–autonomic, and motor neural networks. ACC is structurally (42) and functionally (14) heterogeneous. The existence of motor, cognitive and affective subdivisions of ACC in healthy subjects has been revealed in previous tasked-based neuroimaging studies (14). And with the use of the rs-FCN approach, the presence of rostral ACC-based affective network and caudal ACC-based fronto-parietal attention networks and reciprocal relationship between them was already elucidated in healthy subjects (43).

In case of OCD, the functional heterogeneity of ACC, which has been demonstrated in the multiple task-based fMRI studies with contradictory findings (44), has not yet been investigated using the unique rs-FCNs methodology. For ACC-centered connectivity in OCD, one of our recent study found out weakened rs-FCN between the posterior cingulate cortex (PCC) and subcallosal ACC (Brodmann area (BA) 24) in DMN (45), the clinical importance of which not elucidated yet. In addition, not only the weakened rs-FCN strength between dorsal ACC (BA 24) and right OFC in adult OCD patients (46) but also the decreased rs-FCN strength between rostral ACC and caudate head in child OCD patients (mean age 11.0 years old) (47) showed correlations with higher Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. But rs-FCN approaches for OCD with regard to the cytoarchitectonic/functional sub-regions of ACC as well as their cognitive implications are rare.

In this study, we used rs-FCN approach using MRI to investigate changes in topological organization in intrinsic or spontaneous brain activities in top–down control networks in patients with OCD. We separately examined the FCs of five selected seed regions of interest (ROIs) systematically placed throughout the ACC. And we also made all subjects to conduct five neuropsychological tests measuring diverse dimensions of the executive function. Finally, we analyzed the correlations between the derangements of ACC-seeded rs-FCN subdivision versus neuropsychological test performances. In this study, we hypothesized that the ACC seed-based rs-FCN would show disrupted strength in OCD. This altered strength of functional connectivity could be a reflection of inefficient information processing in OCD, which might correlate with the performance level of neuropsychological tests for executive function measurement.

MATERIALS AND METHODS

1. Subjects

All subjects included in this study had participated in our previous functional magnetic resonance imaging (fMRI) study using AFNI software (http://afni.nimh.nih.gov/afni) (45), from which one OCD patient was not involved in this study because of technical restraints in fMRI image preprocessing using Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm). Twenty-one patients (15 men and six women) who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for OCD, as diagnosed using the Structured Clinical Interview for DSM-IV (SCID-IV), were recruited from the OCD clinic at Seoul National University Hospital. Fifteen patients were drug-naive, and the remaining six had been drug-free for at least 4 weeks at inclusion. Twenty-two gender- and age-matched healthy controls were also recruited. The SCID Non-patient Version (SCID-NP) was used to assess psychiatric disorders in controls. Exclusion criteria included a lifetime history of major psychiatric disorders, significant head injury, seizure disorder, or mental retardation. The current study was approved by the Institutional Review Board at Seoul National University Hospital, and written informed consent was obtained from all subjects after the procedures had been fully explained.

2. Clinical and Neuropsychological Assessments

Obsessive-compulsive symptom severity was measured with the 10-item clinician-rated Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (48). The Beck Depression Inventory (BDI) (49) and the Beck Anxiety Inventory (BAI) (50) were also administered to measure the severity of depression and anxiety, respectively. The Korean version of the Wechsler Adult Intelligence Scale (K-WAIS) (51) was administered to measure the IQ.

To measure the degrees of the executive dysfunction which might be the manifestation of dysfunctional CBTC loop in the OCD (11), we used 5 neuropsychological tests (52, 53) in this study: the Wisconsin Card Sorting Test (WCST), the Controlled Oral Word Association Test (COWAT), the Stroop Color-Word Test (SCWT), Part A and B of the TMT and the RCFT.

The WCST measures the executive function of abstract reasoning, concept formation and attentional set shifting in clinical populations including the OCD patients (54). In this study, we used the conventional WCST form (55) for test administration and scoring. In the Heaton's version, subjects are required to find the correct classification principle for color, form or number cards by way of trial, error and examiner feedback. Once the subject chooses the correct rule, they must maintain this sorting principle (or set) across changing stimulus conditions. Then the classification principle changes after ten consecutive correct responses without warning to the subjects, and the sorting process continues until all cards are sorted or a maximum of six correct sorting criteria have been reached. During these process of card sorting, perseverative responses of sorting the cards consecutively in the same way or repeating the previous principle (56), is selected in this study as a proper measure of so called 'frontal executive functioning' (57).

The COWAT performance reveals the degree of verbal fluency, which requires properly organized verbal retrieval, ongoing monitoring of the verbal search set in working memory and inhibition of inappropriate responses (58). We used 'Category Fluency' score as a representative score of cognitive flexibility in this study.

The SCWT color-word page provides conflicting visual stimuli to measure the executive function of selective attention and response inhibition, which is well reflected in reaction time (59).

The TMT (60) from the Halstead–Reitan Neuropsychological Test Battery is a measure of attention and executive function. Drawing on worksheets, individuals must first connect consecutively numbered circles (Part A) and then connect consecutively numbered and lettered circles by alternating the two sequences (Part B). The TMT Part A reflects attention capacity, concentration and psychomotor speed of the subjects, and the TMT part B requires subjects of intact executive function named set-shifting (13).

The RCFT, originally designed by Rey (61) and scored by Osterrieth (62), is one of the neuropsychological tests which has been widely used to evaluate visuospatial constructional ability and visual (non-verbal) memory functions in the clinical population (63). During the procedure of RCFT performance, subjects were instructed to copy the RCFT (64) figure and then draw what they remembered immediately. And for the comprehensive scoring of the RCFT performances in terms of visuo-constructional ability as well as the executive functioning, we used the Boston Qualitative Scoring System (BQSS) (65), which provided us with the 17 kinds of qualitative scores and 6 summary scores. In this study, we have chosen the Organization Summary Score, which is the arithmetic sum of the copy condition Fragmentation score (measure of information integration) and Planning score (reflecting the overall planning ability based on the order, placement and overall integtity of the depicted elements), as a representative of the executive function measurement (63).

3. fMRI Image Acquisition

Functional images were acquired using a 1.5 T MAGNETOM Avanto scanner (Siemens, Erlangen, Germany). For the resting state with no task performances, functional scans for the whole brain were acquired in 25 contiguous axial slices approximately parallel to the anterior-posterior commissure plane with interleaved multi-slice echo-planar imaging according to the following parameters: TR = 2.34 s, TE = 52 ms, field of view = 22 cm, flip angle = 90°, voxel size = 3.44 × 3.44 × 5 mm, slice thickness = 5 mm, no inter-slice gap.

The resting state fMRI scanning procedure consisted of 120 volumes during 4.68 min. During these resting state experiments, subjects were lying in the dark with their eyes closed, with instructions to relax as much as possible and think about nothing in particular. Meanwhile, the spontaneous brain activity level of each subject was measured throughout the experimental period. Additionally, T1-weighted high-resolution structural images, obtained using a magnetization-prepared rapid acquisition gradient echo sequence, were acquired in 176 contiguous axial slices to co-register and normalize the echo-planar images to the Montreal Neurologic Institute (MNI) template. Imaging parameters for these structural images were as follows: TR = 1.16 s, TE = 4.76 ms, field of view = 23 cm, flip angle = 15°, voxel size = 0.45 × 0.45 × 0.90 mm, slice thickness = 0.9 mm, no inter-slice gap.

4. fMRI Preprocessing

Functional data were preprocessed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm).. The first four volumes of the functional images were removed to eliminate the non-equilibrium effects of magnetization. Preprocessing steps included slice-timing correction for interleaved acquisition, head motion correction, spatial normalization into standard stereotactic MNI spaces with re-sampling to 3-mm cubic voxels, and spatial smoothing using a Gaussian kernel of 6-mm full width at half maximum.

The following additional preprocessing steps were performed for the resting state functional connectivity analysis (66). The resting-state fMRI Data Analysis Toolkit (REST version 1.5, http://resting-fmri.sourceforge.net) was then used to remove the linear trend of time courses and for temporal band-pass filtering (0.01Hz<f < 0.08Hz), as a major research interest with regard to the resting-state fMRI is in slow-changing temporal activation. Before the correlation analysis, signals from the regions of no interest and the first temporal derivatives (head motion parameters, global, white matter, and cerebrospinal fluid signals) were regressed out to reduce spurious correlations derived from cardiac and respiratory fluctuations (67, 68).

5. Functional Connectivity: Seed Generation

We examined the FCs of five selected seed regions of interest (ROIs) out of 16 seed ROIs systematically placed throughout the ACC in two arrays designated superior (S) and inferior (I), following the methods outlined in other study (43). These five ACC seeds selected in the present study refer to the samples of five domains of the self-regulatory functions associated with the ACC; namely, motor control, attention/cognitive control, conflict monitoring, mentalizing, and emotional regulation (69). Seed S1 (MNI coordinates: x = 5, y = -10, z = 47), located in the paracentral lobule and corresponding to BA 31, is in the caudal ACC. The dorsal ACC (dACC), the location of Seed S3 (x = 5, y = 14, z = 42) is in the BA 32. Seed S5 (x = 5, y = 34, z = 28) is located in the rostral section of the supragenual ACC. Seed S7 (x = 5, y = 47, z = 11), which resides in the medial frontal gyrus of BA 32, corresponds to the perigenual ACC. Finally, Seed I9 ($x = 5$, $y = 25$, $z = -10$) is located in the subgenual ACC, corresponding to BA 32.

6. Functional Connectivity Map Generation

Using the "functional connectivity" function of REST, we examined rs-FC maps of the five predefined ACC seed ROIs for each subject. Each spherical seed had a radius of 3 mm in a 3 x 3 x 3 mm voxel-sized space. For each participant, we calculated the mean time series of each seed ROI by averaging across all voxels within the seed. A correlation map for each seed was produced by computing the correlation coefficients voxel-wise. Finally, the correlation coefficient maps were converted into z maps by Fisher's z transform to improve normality.

7. Statistical Analysis

The demographic and clinical data for the OCD and control groups were compared with independent *t*-tests for continuous variables and chi-square tests for categorical variables using PASW 18.0 (SPSS Inc., Chicago, IL, USA).

To reveal within-group functional connectivity patterns, we entered each single-subject intrinsic network component into a voxel-wise one-sample *t*-test in SPM8 to create statistical z maps of the intrinsic networks based on each of the five ACC seeds (uncorrected $p < 0.001$, $k > 10$). After obtaining the regions constituting the intrinsic organization for each group, a binary mask was created using the ImCalc toolbox in SPM8, separately for both groups. Then, a combined mask was generated by combining these two masks.

Differences in the rs-FCNs between the OCD group and the control group were analyzed using two-sample *t*-tests, with a previously described masking procedure, to avoid detection of clusters that did not appear in the ACC network map. The resulting statistical maps are presented according to the threshold of uncorrected $p < 0.001$ and a cluster threshold of $k > 10$ for multiple comparisons, which corresponds to the corrected threshold of $p < 0.05$, as determined by AlphaSim in AFNI (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

Correlation coefficients (Z scores) of specific clusters with significantly different rs-FC strengths between the two groups were extracted using the MarsBar toolbox (http://marsbar.sourceforge.net) to test the relationship between rs-FC strength versus neuropsychological test performance and Y-BOCS scores (total score, obsession subscale and compulsion subscale) in the OCD group. Pearson's simple correlation coefficient was used to investigate the associations between these five ACC seed-related rs-FC strengths versus several neuropsychological test sub-scores measuring executive functioning and Y-BOCS scores. To fully explore the possibility of the ACC-based rs-FCNs as a biomarker reflecting executive dysfunction and obsessive-compulsive symptomatology in OCD patients, we admitted a more exploratory threshold of $p < 0.05$ (uncorrected, two-tailed) rather than the strict threshold drawn by the Bonferroni–Holms procedure. And post-hoc analyses to examine the impact of some clinical variables of BDI and BAI scores rs-FCN alteration were conducted, as these two variables showed significant differences between the OCD group and healthy controls.

RESULTS

1. Demographic and Clinical Characteristics

The demographic and clinical characteristics of the subjects are presented in Table 1 and 2. We found no significant differences between the groups regarding age, gender, years of education and IQ. In contrast, significant differences were observed between the OCD group and the control group for the BAI and BDI scores ($p < 0.05$, two-tailed)

In this study, no significant differences were observed in RCFT organization score and COWAT category fluency score. In contrast, the OCD group and control group showed significant differences in the the WCST perseverative response score, the SCWT reaction time, and reaction time for TMT part A/B ($p < 0.05$, two-tailed).

Table 1. Demographic and clinical characteristics of OCD group and healthy control

	OCD (n=21)	Healthy control (n=22)	t-score	p-value
Demographic characteristics				
Age(year)	25.10±7.13	24.36±4.02	0.412	0.683
Gender(M/F)	15/6	16/6	-	-
Education(year)	14.38±3.81	14.41±1.62	-0.031	0.975
Estimated IQ	108.57±13.12	112.50±13.05	-0.961	0.343
Illness duration (year)	7.39±5.45	-	-	-
Clinical rating scales				
Y-BOCS score				
Obsession	11.48±4.52	-	-	-
Compulsion	10.33±4.59	-	-	-
Total score	21.81±6.96	-	-	-
BAI score	18.57±15.02	4.05±5.20	4.177	<0.001*
BDI score	16.52±11.01	3.65±4.93	4.870	<0.001*

Abbreviations: OCD: obsessive-compulsive disorder; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory.

Data are given as mean ± standard deviation.

* $p<0.05$

Table 2. Neuropsychological test scores of the subjects

	OCD (n=21)	Healthy control (n=22)	t-score	p-value
WCST Perseverative response	9.05±4.02	6.45±3.07	2.386	0.022*
COWAT category fluency	38.81±8,94	41.41±9.26	-0.936	0.355
SCWT RT	109.33±21.71	89.23±26.52	2.713	0.010*
TMT-B RT	75.10±31.94	56.05±17.17	2.452	0.019*
TMT-A RT	33.10±12.76	24.14±7.19	2.77	0.010*
RCFT organization score	6.62±1.24	6.86±1.17	-0.665	0.510

Data are given as mean ± standard deviation. *p<0.05

Abbreviations: OCD: Obsessive-Compulsive Disorder; WCST: Wisconsin Card Sorting Test; COWAT: Controlled Oral Word Association Test; SCWT: Stroop Color Word Test; TMT: Trail Making Test; RCFT: Rey-Osterrieth Complex Figure Test

2. Resting State Functional Connectivity

Overall, both the OCD and control groups exhibited a distinct segregation of ACC in rs-FCNs along the rostro-caudal axis, which matched with previous studies on functional differentiation within the ACC (43, 69). The specific intra-group and inter-group findings for each of the ACC seed regions are described below. And rs-FCN maps of the OCD group for each five of ROI seeds are presented as separated figures (Figure 1 for S1 seed; Figure 2 for S3 seed; Figure 3 for S5 seed; Figure 4 for S7 seed; and Figure 5 for I9 seed).

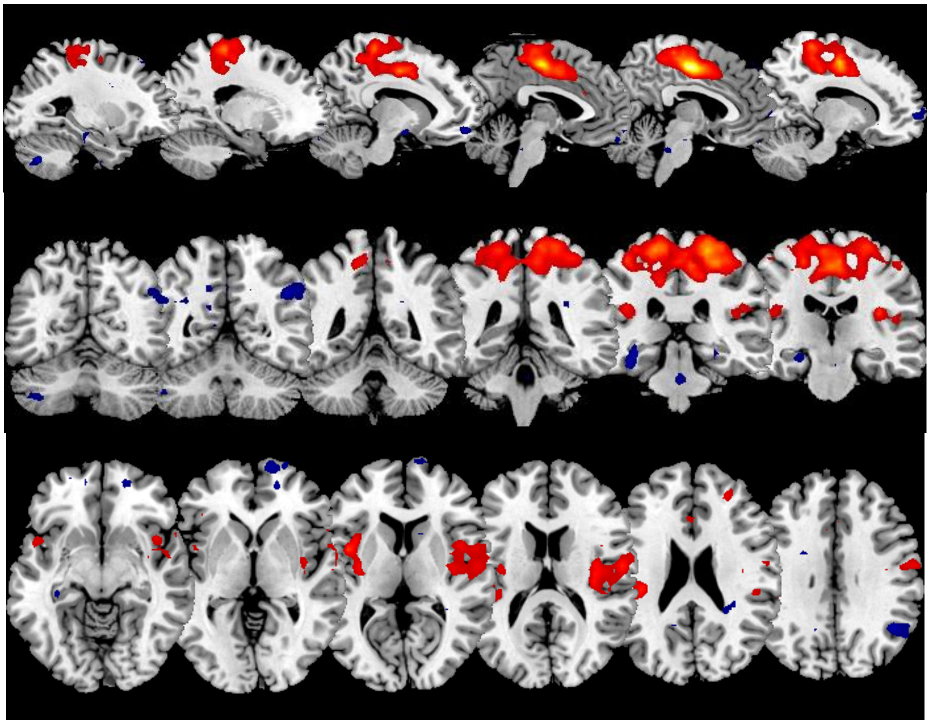


Figure 1. Positive (depicted with red) and negative (depicted with blue) resting state functional connectivity networks between the S1 ACC seed region and other brain area in Obsessive-Compulsive Disorder group. Results are displayed at $P < .001$, uncorrected.

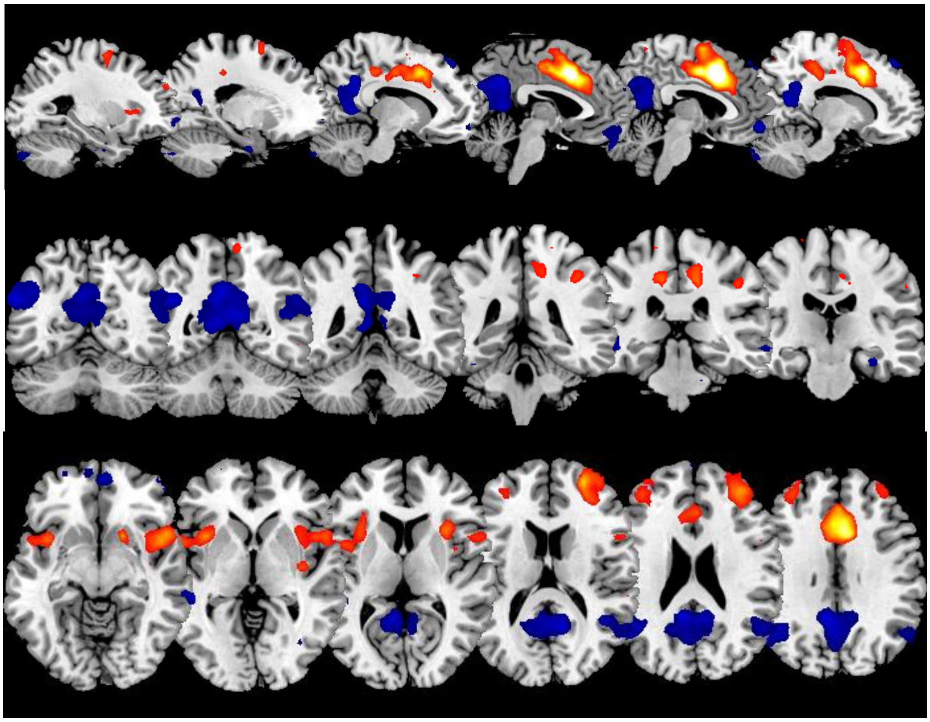


Figure 2. Positive (depicted with red) and negative (depicted with blue) resting state functional connectivity networks between the S3 ACC seed region and other brain area in Obsessive-Compulsive Disorder group. Results are displayed at P < .001, uncorrected.

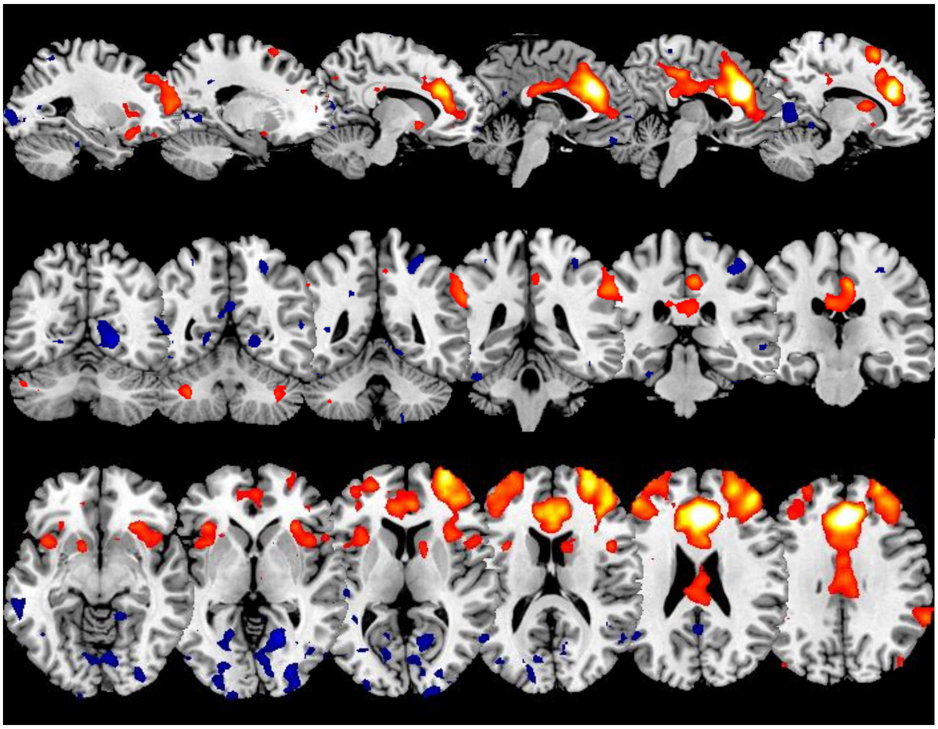


Figure 3. Positive (depicted with red) and negative (depicted with blue) resting state functional connectivity networks between the S5 ACC seed region and other brain area in Obsessive-Compulsive Disorder group. Results are displayed at $P < .001$, uncorrected.

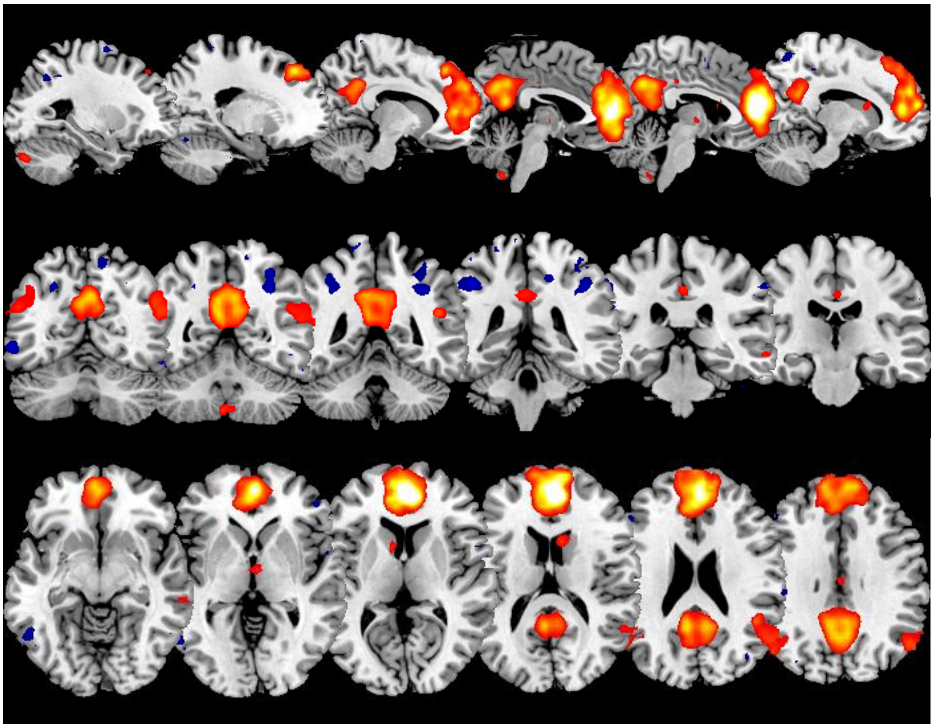


Figure 4. Positive (depicted with red) and negative (depicted with blue) resting state functional connectivity networks between the S7 ACC seed region and other brain area in Obsessive-Compulsive Disorder group. Results are displayed at $P < .001$, uncorrected.

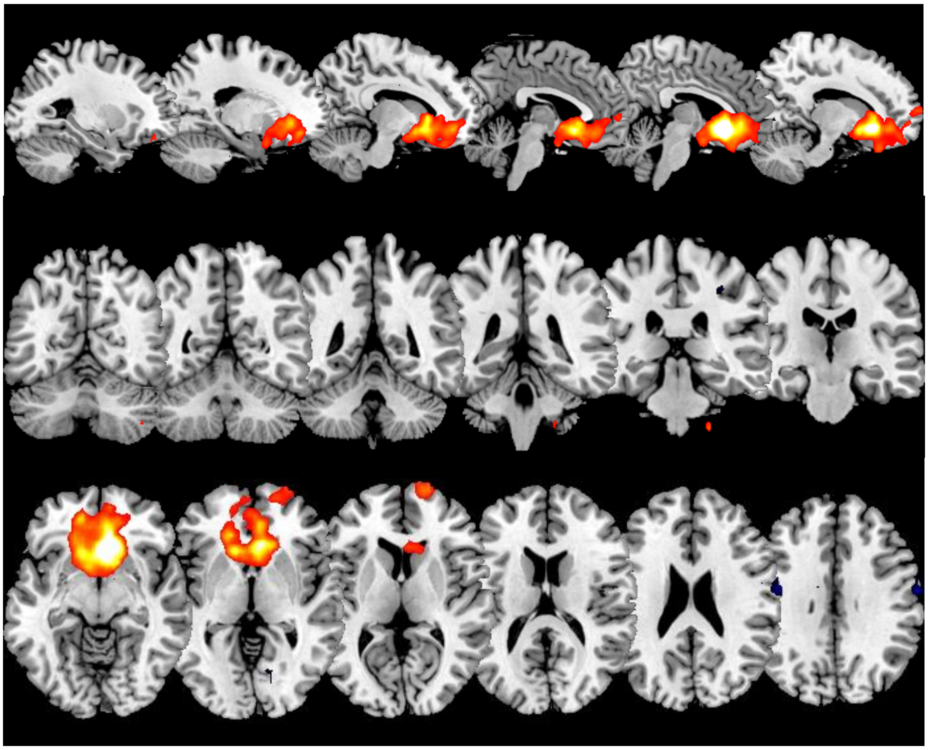


Figure 5. Positive (depicted with red) and negative (depicted with blue) resting state functional connectivity networks between the I9 ACC seed region and other brain area in Obsessive-Compulsive Disorder group. Results are displayed at $P < .001$, uncorrected.

2.1. Five ACC Seed-Related rs-FCNs: Overlapping Findings of positive correlation

Caudal Seed S1 in the patients with OCD and healthy controls correlated with a network of premotor and supplementary motor areas (BA 6), the primary somatosensory cortex (BA 3), the dorsal ACC (BA 24/32), the primary motor cortex (BA 4), the pars opercularis (BA 44), the insula (BA 13), the posterior cingulate cortex (PCC) (BA 31), the claustrum, and the paracentral lobule (BA 5) (Figure 1 and 6).

Seed S3, which resides in the dorsal ACC, demonstrated significant rs-FC in the caudal ACC (BA 24/32), PCC (BA 31), premotor and supplementary motor area, precuneus (BA 7), postcentral gyrus (BA 7), primary motor cortex, primary somatosensory cortex (BA 1/2/3), orbitofrontal cortex (OFC) (BA 10/47), superior temporal gyrus (BA 22), claustrum, supramarginal gyrus of the inferior parietal lobule (IPL) (BA 40), Broca's area (BA 44/45), insula, primary auditory cortex (BA 42), putamen, and dorsolateral prefrontal cortex (DLPFC) (BA 9) in both groups (Figure 2 and 6). These results are in accordance with the previous functional connectivity findings (70).

The rostral ACC seed region S5 in both groups showed significant rs-FC with the OFC (BA 10/11/ 47), DLPFC (BA 8/9/46), premotor area, Broca's area, caudal/dorsal/perigenual ACC (BA 32), PCC (BA 23/31), caudate body, putamen, claustrum, insula, precuneus (BA 7), supramarginal gyrus of the IPL, superior occipital gyrus (BA 19), and tonsil/tuber of the cerebellum (Figure 3 and 6).

Perigenual ACC Seed S7 in both groups revealed rs-FC with the OFC (BA 10/47), DLPFC (BA 8/9), pregenual (BA 33)/ventral (BA 24)/perigenial (BA 32) ACC, premotor cortex, subcallosal gyrus (BA 34), precuneus (BA

7/19/31), PCC (BA 23/31), superior parietal lobule (BA 7), angular (BA 39) and supramarginal gyrus (BA 40) of the IPL, Wernicke's area (BA 22), temporal pole (BA 38), fusiform gyrus (BA 20), insula, middle (BA 21) and inferior (BA 20/21) temporal cortices, head/body of the caudate, thalamus, and culmen/pyramis/inferior semi-lunar lobule of the cerebellum (Figure 4 and 6).

Seed I9, located in the subgenual ACC, was associated with an extensive pattern of correlated activity in the OFC (BA 10/11), pars opercularis, perigenual (BA 32) /subgenual (BA 25) ACC, subcallosal gyrus, middle (BA 19) and inferior (BA 20) temporal cortices, uncus (BA 34/38), caudate head, tonsil and pyramis of the cerebellum in both groups (Figure 5 and 6).

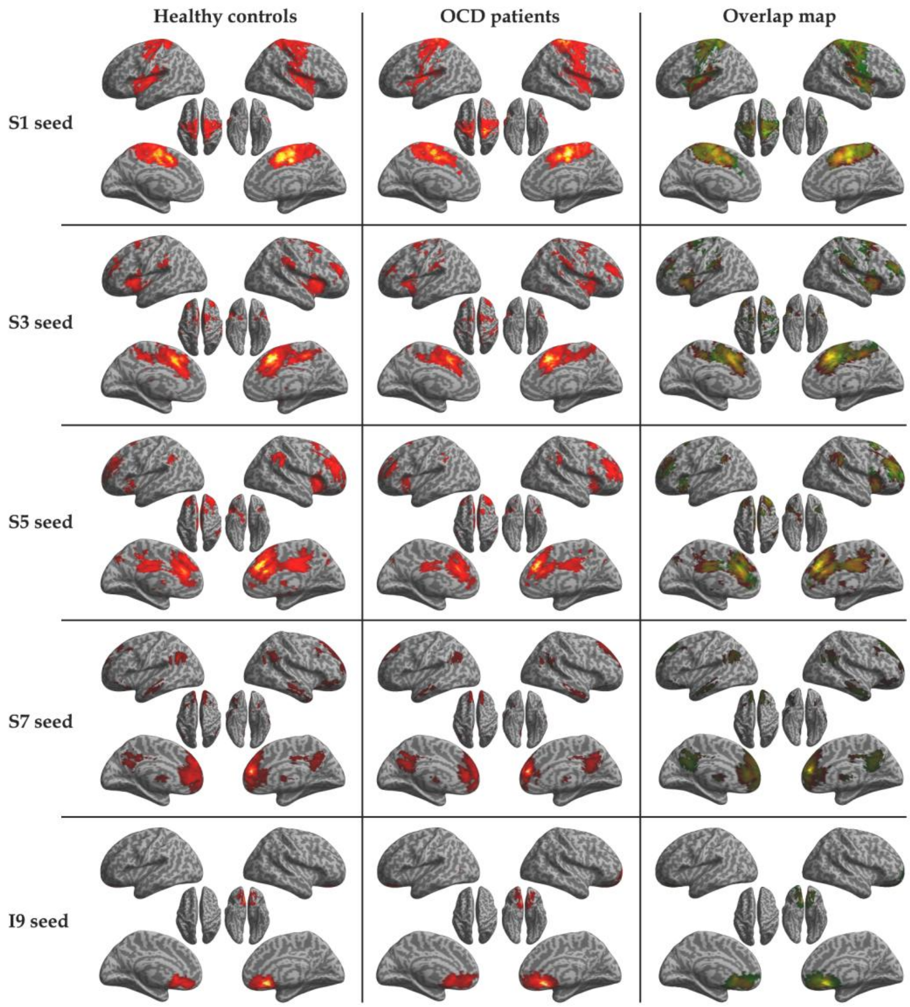


Figure 6. Positive resting state functional connectivity networks of the 5 ACC seed ROIs in OCD and healthy control. Significant within-group functional connectivity maps of the 5 ACC seeds are placed on 3-dimensional anatomical images. Results are displayed at $P < .001$, uncorrected.

2.2. Five ACC Seed-Related rs-FCNs: Between-Group Analyses of positive correlation

Between-group analyses revealed that the rs-FC between the ACC S1 seed and the left claustrum, between the ACC S3 seed and the left pulvinar thalamus, between the ACC S5 seed and the right claustrum, and between the ACC S7 seed and the right IPL were significantly weaker in the OCD group. In contrast, the rs-FC between the ACC I9 seed and the right OFC was significantly stronger in the OCD group ($p < 0.001$, $k > 10$) (Figure 7, Table 3). When additional multiple regression analyses (forced entry method) which put forward BDI, BAI scores as well as the 'diagnosis' as predictor variables were performed, no predictor variables other than the 'diagnosis' survived the statistical significance threshold of $p < .05$ (Table 4).

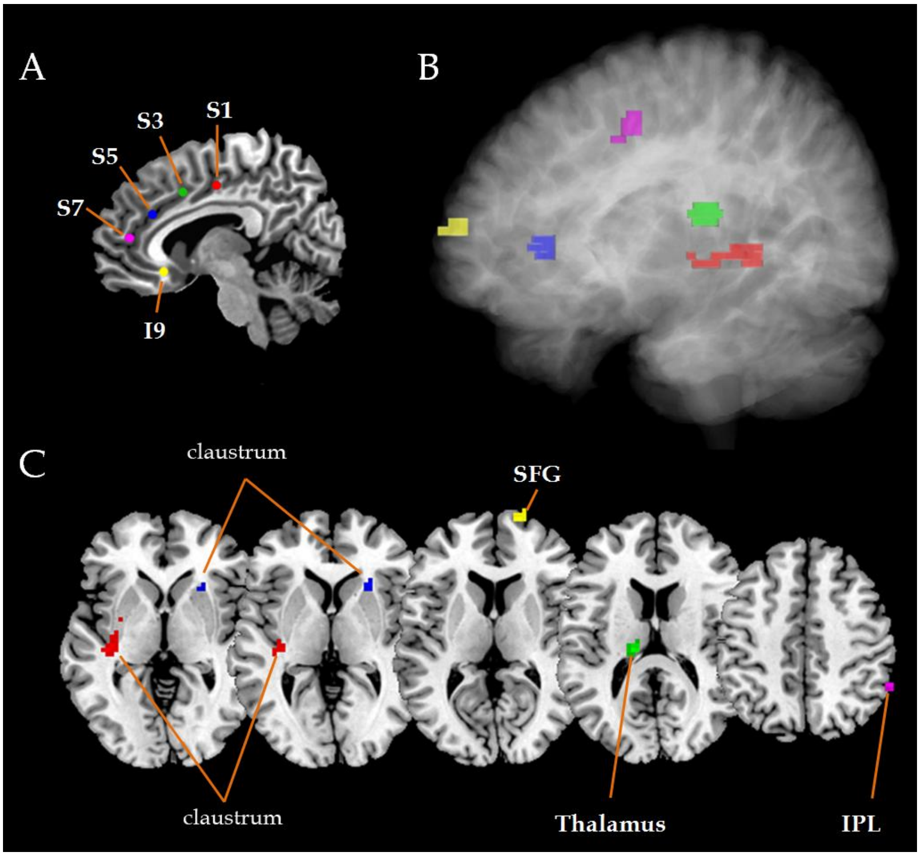


Figure 7. Significant between-group (main effect) differences in positive rs-FCNs of the 5 ACC seed ROIs. The results are placed on (A) 3-dimensional, (B) 2-dimensional and (C) anatomical brain images. Colored overlays correspond regions demonstrating weaker functional connectivity in OCD patients, with respect to red (S1), green (S3), blue (S5) and pink (S7); yellow, regions depicting stronger functional connectivity with the respective ACC I9 seed region in patients vs controls. Results are displayed at $P < .001$, uncorrected.

Table 3. Regional difference in resting state functional connectivity network between the patients with OCD and healthy controls

brain region	laterality	BA	Peak coordinates (MNI)			T score	Z score	p value	cluster size
			X	y	z				
S1_R: control>OCD									
Claustrum	L	-	-39	-24	0	4.24	3.84	<0.001	29
S3_R: control>OCD									
thalamus, pulvinar	L	-	-15	-24	15	4.87	4.3	<0.001	21
S5_R: control>OCD									
Claustrum	R	-	27	21	3	4.34	3.92	<0.001	12
S7_R: control>OCD									
Supramarginal gyrus	R	40	60	-48	48	4.49	4.02	<0.001	11
I9_R: OCD>control									
Frontopolar cortex	R	10	18	66	9	3.81	3.5	<0.001	11

Abbreviations: BA: Brodmann area; MNI: Montreal Neurological Institute; OCD: Obsessive-compulsive disorder; L: left; R: right.

The thresholds of statistical significance in between-group analyses were set to $p < 0.001$ (uncorrected) and k (voxel threshold) > 10.

Table 4. Significance of diagnosis in predicting strength of positive resting state functional connectivity*

	R^2 (p value)	Predictor variables	B	SE B	t score	p value
S1 vs. Lt. claustrum	0.438	Diagnosis	-0.168	0.054	-3.077	0.004†
	(p<.001†)	BDI	-0.002	0.003	-0.456	0.651
		BAI	-0.002	0.003	-0.930	0.358
S3 vs. Lt. pulvinar	0.387	Diagnosis	-0.218	0.068	-3.224	0.003†
	(p<.001†)	BDI	-0.007	0.004	-1.628	0.112
		BAI	0.004	0.003	1.313	0.197
S5 vs. Rt. Claustrum	0.411	Diagnosis	-0.253	0.054	-4.701	<0.001†
	(p<.001†)	BDI	0.005	0.003	1.541	0.132
		BAI	-0.001	0.003	-0.519	0.607
S7 vs. Rt. supramarginal gyrus	0.355	Diagnosis	-0.242	0.083	-2.900	0.006†
	(p=.001†)	BDI	0.003	0.005	0.660	0.513
		BAI	-0.006	0.004	-1.482	0.146
I9 vs. Rt. frontopolar cortex	0.274	Diagnosis	0.329	0.095	3.446	0.001†
	(p=.005†)	BDI	-0.006	0.006	-1.084	0.285
		BAI	0.002	0.004	0.357	0.723

*Results were obtained from multiple regression analyses also including BDI/BAI score as predictors. †p< .05.

Abbreviations: BAI= Beck Anxiety Inventory; BDI= Beck Depression Inventory; Lt.= left; Rt.= right; R^2= coefficient of determination; SE= standard error

2.3. Five ACC Seed-Related rs-FCNs: negative correlation

There were also marked distinctions in negative relationships ("anticorrelations") between ACC and other brain regions, with systematic variations along the axis of rostral to caudal portions of ACC.

The subgenual seed I9, and superior rostral seed S7 negatively predicted activity within a number of posterior brain regions linked to sensorimotor and attentional domains, including superior, inferior and posterior parietal regions, temporal cortices, portions of extrastriate and striate visual cortices, and superior cerebellar regions for both groups of OCD and HC, with no significant differences in the rs-FC anti-correlation strength between these two groups (Table 5).

Centrally located superior seed s5 negatively predicted activity within portions of the occipito-temporal lobes and superior, posterior and parietal lobes in the HC group. In contrast, these patterns of anti-correlations regarding S5 seed were less distinctive in the OCD group, especially for the brain regions of right fusiform gyrus (BA 18), right associative visual cortex (BA 19) and left primary somatosensory cortex (BA 2) (uncorrected $p<.001$, $k>10$) (Table 5).

In case of caudally located ACC seeds of s1 and s3, negatively predicted activity was extended to the whole areas of frontal lobe - many of the same regions positively predicted by extreme rostral seeds – as well as in the posterior cerebral cortices. However, inter-group differences in the strength of anti-correlation were located in the temporo-occipital and cerebellar cortices, as OCD group showed more attenuated rs-FC anti-correlation between s3 seed versus right parahippocampal gyrus (BA 19), right lingual gyrus (BA 18), left associative visual cortex (BA 19) and cerebellum (right culmen). For the extremely caudal-located seed s1, significantly attenuated rs-FC anti-correlation in the OCD group was not found (uncorrected $p<.001$, $k>10$) (Table 5).

When additional multiple regression analyses (forced entry method) which put forward BDI, BAI scores as well as the ‘diagnosis’ as predictor variables were performed, no predictor variables other than the ‘diagnosis’ survived the statistical significance threshold of $p < .05$ (Table 6).

Table 5. Regional difference in negative correlations of resting state functional connectivity network between the patients with obsessive-compulsive disorder and healthy controls

brain region	laterality	BA	Peak coordinates (MNI)			T score	Z score	p value	cluster size
			x	y	z				
S1_R: NS									
S3_R: control>OCD									
Culmen of cerebellum	R	-	18	-42	-9	4.39	3.95	<0.001	36
Parahippocampal gyrus	R	19	21	-48	0	3.85	3.54	<0.001	
Associative visual cortex	L	19	-27	-87	9	4	3.66	<0.001	15
Lingual gyrus	R	18	24	-75	-6	3.61	3.34	<0.001	11
S5_R: control>OCD									
Fusiform gyrus	R	18	24	-87	-15	4.44	3.99	<0.001	11
Associative visual cortex	R	19	39	-78	24	4.39	3.95	<0.001	14
Primary somatosensory cortex	L	2	-45	-33	63	4.37	3.93	<0.001	28
S7_R & I9_R: NS									

Abbreviations: BA: Brodmann area; MNI: Montreal Neurological Institute; OCD: Obsessive-compulsive disorder; L: left; R: right.

The thresholds of statistical significance in between-group analyses were set to $p < 0.001$ (uncorrected) and k (voxel threshold) > 10.

Table 6. Significance of diagnosis in predicting strength of negative resting state functional connectivity*

	R^2 (p value)	Predictor variables	B	SE B	t score	p value
S3 vs. Rt. Parahippocampal gyrus	0.356	Diagnosis	0.325	0.075	4.317	<0.001†
	(p=.001†)	BDI	-0.004	0.005	-0.883	0.382
		BAI	-0.001	0.004	-0.286	0.776
S3 vs. Lt. associative visual cortex	0.276	Diagnosis	0.278	0.082	3.385	0.002†
	(p=.005†)	BDI	-0.004	0.005	-0.726	0.472
		BAI	0.001	0.004	0.161	0.873
S3 vs. Rt. Lingual gyrus	0.290	Diagnosis	0.282	0.078	3.617	<0.001†
	(p=.004†)	BDI	-0.006	0.005	-1.187	0.243
		BAI	0.001	0.004	0.357	0.723
S5 vs. Rt. Fusiform gyrus	0.388	Diagnosis	0.302	0.065	4.640	<0.001†
	(p<.001†)	BDI	-0.007	0.004	-1.805	0.079
		BAI	0.001	0.003	0.452	0.654
S5 vs. Rt. Visual associative cortex	0.357	Diagnosis	0.245	0.075	3.279	0.002†
	(p=.001†)	BDI	-0.006	0.005	-1.210	0.233
		BAI	0.005	0.003	1.571	0.124
S5 vs. Lt. primary somatosensory cortex	0.383	Diagnosis	0.179	0.064	2.789	0.008†
	(p<.001†)	BDI	-0.001	0.004	-0.297	0.768
		BAI	0.004	0.003	1.497	0.142

- Results were obtained from multiple regression analyses also including BDI/BAI score as predictors. †p< .05

Abbreviations: BAI= Beck Anxiety Inventory; BDI= Beck Depression Inventory; Lt.= left; Rt.= right; R^2= coefficient of determination; SE= standard error

2.3. Correlations between altered rs-FCNs versus Y-BOCS scores

For the regions showing significant differences in functional connectivity strength between OCD patients and controls, increased positive rs-FC strength between ACC Seed S5 and the right claustrum correlated with higher Y-BOCS total score (r=.548, p=.010) and Y-BOCS Compulsion subscale (r = 0.497, p = 0.022) in the OCD group. Regarding the Y-BOCS Obsession subscale, stronger positive rs-FC between the ACC S1 seed versus left claustrum could predict lower Y-BOCS Obsession subscale in OCD patients (r=-.487, p=.025) (Figure 8, Table 7). In terms of the negative rs-FCNs, stronger negative rs-FC berween the ACC S3 seed versus right parahippocampal gyrus showed correlations with lesser compulsive symptomatology masured using the Y-BOCS Compulsion subscale (r=.481, p=.027) (Figure 9, Table 7). No other statistically significant correlations between ACC seed-based regional rs-FC strength versus Y-BOCS scores were found ($p < 0.02$, two-tailed).

Table 7. Correlation between altered regional resting state functional connectivity strength versus Y-BOCS scores in Obsessive-Compulsive disorder subjects

rs-FCN		Obsession	Compulsion	Total
Positive correlation				
S1 vs. Lt. claustrum	Correlation	-0.487	0.123	-0.236
	Significance	0.025*	0.597	0.303
S3 vs. Lt. pulvinar	Correlation	0.186	-0.133	0.033
	Significance	0.420	0.565	0.887
S5 vs. Rt. Claustrum	Correlation	0.340	0.497	0.548
	Significance	0.132	0.022*	0.010*
S7 vs. Rt. Supramarginal gyrus	Correlation	-0.205	-0.066	-0.177
	Significance	0.373	0.776	0.444
I9 vs. Rt. frontopolar cortex	Correlation	-0.171	-0.065	-0.154
	Significance	0.459	0.780	0.506
Negative connectivity				
S3 vs. Lt. associative visual cortex	Correlation	-0.049	0.018	-0.019
	Significance	0.834	0.937	0.933
S3 vs. Rt. Lingual gyrus	Correlation	-0.046	0.171	0.083
	Significance	0.845	0.459	0.721
S3 vs. Rt. parahippocampal gyrus	Correlation	-0.291	0.481	0.128
	Significance	0.200	0.027*	0.581
S5 vs. Lt. primary somatosensory cortex	Correlation	0.294	-0.05	0.158
	Significance	0.196	0.831	0.493
S5 vs. Rt. Fusiform gyrus	Correlation	-0.369	0.044	-0.21
	Significance	0.100	0.849	0.360
S5 vs. Rt. Associative visual cortex	Correlation	0.137	0.107	0.159
	Significance	0.554	0.644	0.490

*p<.05. *Abbreviations:* Lt.= left; rs-FCN= resting state functional connectivity network; Rt.= right; Total= Y-BOCS total score

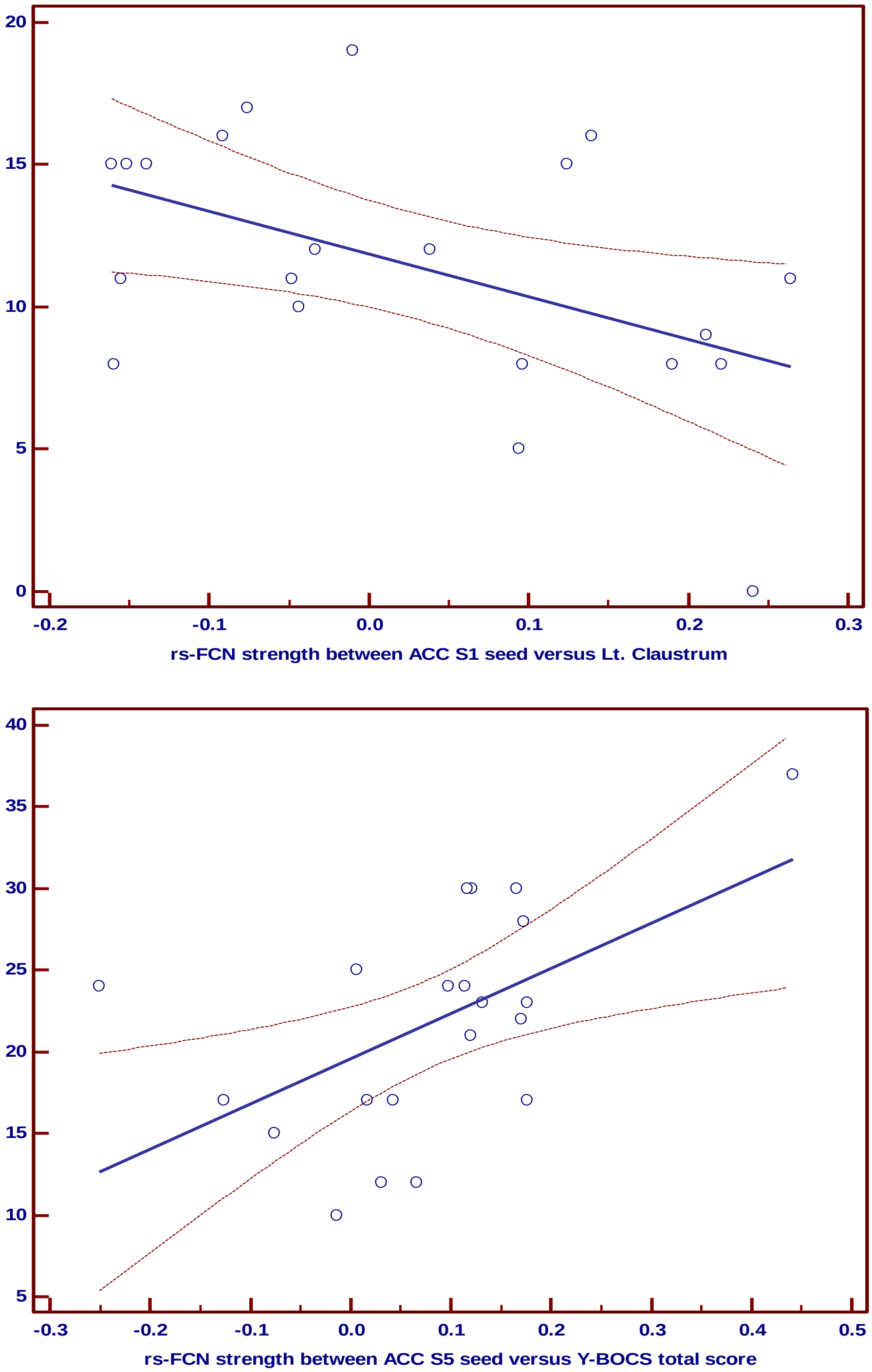


Figure 8. Correlation between positive regional functional connectivity strength and Y-BOCS scores in obsessive-compulsive disorder.

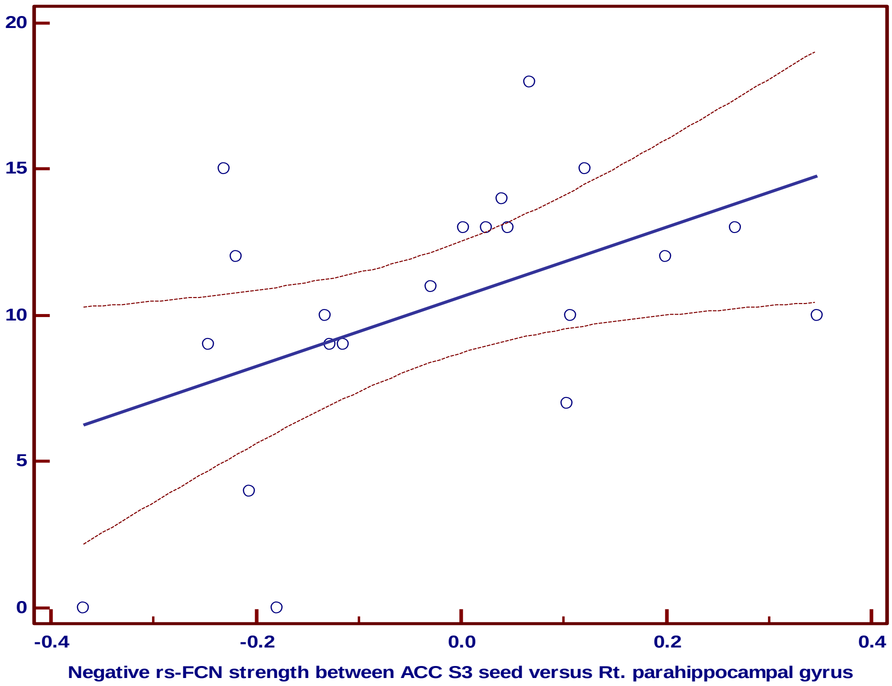


Figure 9. Correlation between negative regional functional connectivity strength and Y-BOCS scores in obsessive-compulsive disorder

2.4. Connectivity Correlations with Neuropsychological Measures

For the regions showing significant differences in functional connectivity strength between OCD patients and controls, increased rs-FC strength between ACC Seed S5 and the right claustrum correlated with higher RCFT organization scores in the OCD group ($r = 0.541$, $p = 0.011$) (Figure 10-(a), Table 8). Prolonged TMT-A reaction time was correlated with weaker rs-FC strength between ACC Seed S7 and the right supramarginal gyrus in the OCD group ($r = -0.520$, $p = 0.019$) (Figure 10-(b), Table 8). In addition, stronger positive rs-FC between the ACC I9 seed versus right frontopolar cortex also indicated shorter reaction time in TMT-A performance, with lower statistical significance ($r=-.458$, $p=.042$) than that of the ACC S7 seed. No other statistically significant correlations between ACC seed-based regional rs-FC strength versus neuropsychological test sub-scores were found ($p < 0.05$, two-tailed) (Table 8). In the healthy control group, lowered positive rs-FC between the ACC S7 seed versus right supramarginal gyrus indicated lesser WCST perseverative response ($r=-.51$, $p=.015$), better COWAT Category fluency performance ($r=.477$, $p=.025$) and the shorter TMT-B reaction time ($r=-.576$, $p=.005$). In addition, stronger positive rs-FC between the ACC S1 seed versus left claustrum indicated more perseverative response during WCST performance ($r=.497$, $p=.019$) (Table 9).

In the OCD group, negative rs-FCN alteration did not demonstrate statistically significant correlations with neuropsychological test performances (Table 10). In contrast, as negative rs-FC between the ACC S3 seed versus right lingual gyrus was weakened, the Category fluency score of COWAT became elevated in the healthy control group ($r=.578$, $p=.005$). ($p<.05$, two-tailed) (Table 11).

Table 8. Bivariate correlations between regional positive functional connectivity strength and neuropsychological test performance in Obsessive-Compulsive disorder patients (n=21)

Resting state functional connectivity network		**WCST**	**COWAT**	**SCWT**	**TMT-B**	**TMT-A**	**RCFT**
S1 vs. Lt. claustrum	Correlation	0.103	0.173	-0.166	0.093	-0.255	-0.136
	Significance	0.658	0.453	0.471	0.689	0.278	0.556
S3 vs. Lt. pulvinar	Correlation	-0.273	0.121	0.078	0.257	-0.151	0.089
	Significance	0.231	0.603	0.737	0.261	0.526	0.703
S5 vs. Rt. Claustrum	Correlation	0.094	-0.099	0.006	0.274	0.397	0.541
	Significance	0.684	0.670	0.981	0.230	0.083	0.011*
S7 vs. Rt. supramarginal gyrus	Correlation	-0.244	0.295	-0.238	-0.310	-0.520	0.086
	Significance	0.286	0.194	0.230	0.171	0.019*	0.710
I9 vs. Rt. frontopolar cortex	Correlation	0.187	0.332	0.008	-0.310	-0.458	0.005
	Significance	0.417	0.142	0.974	0.171	0.042*	0.983

Abbreviation: Correlation= Pearson's correlation coefficient; COWAT= Category fluency score of the Controlled oral word association test; Lt.= left; RCFT= Organization score of the Rey-Osterrieth complex figure test; Rt.= right; TMT-A= Reaction time for Trail-making test A; TMT-B= Reaction time for the Trail-making test B; SCWT= Reaction time for the color-word page of Stroop color word test; WCST= Perseverative response score of Wisconsin card sorting test. *p<.05 (two-tailed)

Table 9. Bivariate correlations between regional positive functional connectivity strength and neuropsychological test performance in healthy controls (n=22)

Resting state functional connectivity network		**WCST**	**COWAT**	**SCWT**	**TMT-B**	**TMT-A**	**RCFT**
S1 vs Lt. claustrum	Correlation	0.497	-0.022	0.066	0.321	0.406	-0.016
	p value	0.019*	0.921	0.771	0.146	0.061	0.945
S3 vs Lt. pulvinar	Correlation	0.004	0.075	0.135	0.039	0.330	0.257
	p value	0.986	0.739	0.549	0.865	0.134	0.248
S5 vs Rt. Claustrum	Correlation	-0.173	0.026	-0.076	-0.214	-0.340	-0.119
	p value	0.441	0.910	0.737	0.339	0.122	0.599
S7 vs Rt. supramarginal gyrus	Correlation	-0.510	0.477	-0.084	-0.576	-0.407	0.116
	p value	0.015*	0.025*	0.710	0.005*	0.060	0.608
I9 vs. Rt. frontopolar cortex	Correlation	0.068	-0.225	0.121	0.223	0.402	0.372
	p value	0.765	0.315	0.591	0.319	0.063	0.089

Abbreviation: Correlation= Pearson's correlation coefficient; COWAT= Category fluency score of the Controlled oral word association test; Lt.= left; RCFT= Organization score of the Rey-Osterrieth complex figure test; Rt.= right; TMT-A= Reaction time for Trail-making test A; TMT-B= Reaction time for the Trail-making test B; SCWT= Reaction time for the color-word page of Stroop color word test; WCST= Perseverative response score of Wisconsin card sorting test. *p<.05 (two-tailed)

Table 10. Bivariate correlations between regional negative functional connectivity strength and neuropsychological test performance in Obsessive-Compulsive disorder patients (n=21)

Resting state functional connectivity network		**WCST**	**COWAT**	**SCWT**	**TMT-B**	**TMT-A**	**RCFT**
S3 vs. Rt. parahippocampal gyrus	Correlation	0.137	-0.082	0.240	0.208	0.043	-0.069
	Significance	0.553	0.723	0.295	0.366	0.857	0.768
S3 vs. Lt. associative visual cortex	Correlation	-0.062	-0.068	-0.364	-0.187	0.065	0.064
	Significance	0.789	0.770	0.105	0.416	0.784	0.784
S3 vs. Rt. Lingual gyrus	Correlation	-0.144	0.316	-0.161	-0.302	-0.258	0.185
	Significance	0.533	0.163	0.487	0.183	0.273	0.422
S5 vs. Rt. Fusiform gyrus	Correlation	-0.154	0.375	-0.245	-0.211	-0.235	-0.266
	Significance	0.506	0.094	0.284	0.358	0.318	0.243
S5 vs. Rt. Associative visual cortex	Correlation	-0.358	0.207	-0.115	0.033	0.054	-0.252
	Significance	0.111	0.367	0.619	0.888	0.820	0.271
S5 vs. Lt. primary somatosensory	Correlation	-0.368	-0.053	0.166	-0.092	-0.038	-0.108
cortex	Significance	0.101	0.819	0.473	0.690	0.873	0.642

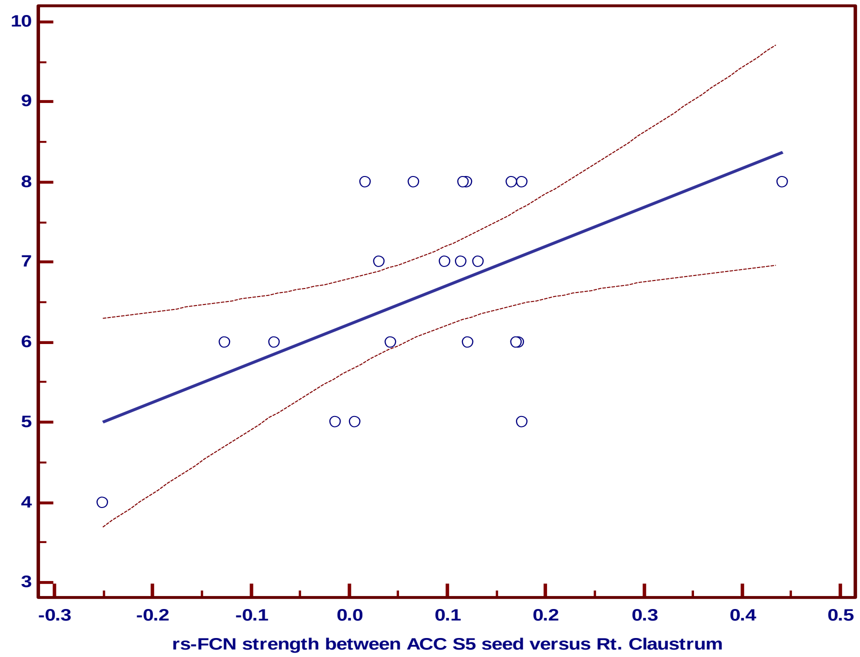
Abbreviation: Correlation= Pearson's correlation coefficient; COWAT= Category fluency score of the Controlled oral word association test; Lt.= left; RCFT= Organization score of the Rey-Osterrieth complex figure test; Rt.= right; TMT-A= Reaction time for Trail-making test A; TMT-B= Reaction time for the Trail-making test B; SCWT= Reaction time for the color-word page of Stroop color word test; WCST= Perseverative response score of Wisconsin card sorting test. *p<.05 (two-tailed)

Table 11. Bivariate correlations between regional negative functional connectivity strength and neuropsychological test performance in healthy controls (n=22)

Resting state functional connectivity network		**WCST**	**COWAT**	**SCWT**	**TMT-B**	**TMT-A**	**RCFT**
S3 vs. Rt. parahippocampal gyrus	Correlation	-0.006	0.205	0.147	-0.253	-0.046	-0.282
	p value	0.979	0.360	0.515	0.255	0.837	0.204
S3 vs. Lt. associative visual cortex	Correlation	-0.184	0.141	0.126	-0.178	-0.194	-0.329
	p value	0.412	0.531	0.575	0.428	0.388	0.135
S3 vs. Rt. Lingual gyrus	Correlation	-0.228	0.578	0.059	-0.398	-0.03	-0.229
	p value	0.307	0.005*	0.794	0.066	0.895	0.305
S5 vs. Rt. Fusiform gyrus	Correlation	0.380	0.216	0.096	0.193	0.222	0.011
	p value	0.081	0.334	0.671	0.388	0.320	0.963
S5 vs. Rt. Associative visual cortex	Correlation	-0.139	0.258	-0.319	0	0.123	-0.126
	p value	0.538	0.247	0.147	>0.999	0.586	0.576
S5 vs. Lt. primary somatosensory	Correlation	0.089	0.155	-0.158	0.195	-0.335	-0.188
cortex	p value	0.694	0.490	0.481	0.385	0.127	0.402

Abbreviation: Correlation= Pearson's correlation coefficient; COWAT= Category fluency score of the Controlled oral word association test; Lt.= left; RCFT= Organization score of the Rey-Osterrieth complex figure test; Rt.= right; TMT-A= Reaction time for Trail-making test A; TMT-B= Reaction time for the Trail-making test B; SCWT= Reaction time for the color-word page of Stroop color word test; WCST= Perseverative response score of Wisconsin card sorting test. *p<.05 (two-tailed)

(a)



(b)

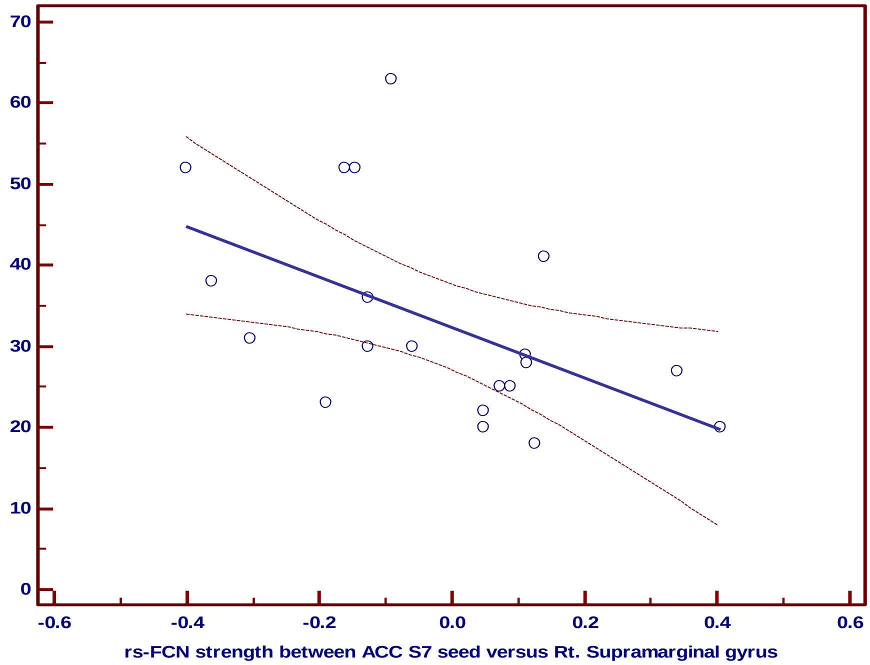


Figure 10. Correlation between regional functional connectivity strength and neuropsychological test performance in obsessive-compulsive disorder. Stronger functional connectivity (a) between the ACC S5 seed region and the right claustrum predicted higher RCFT organization scores (r=0.541, p

= 0.011). And stronger functional connectivity (b) between ACC S7 seed region and the right supramarginal gyrus could predict shorter reaction time in TMT-A performance (r=-0.520, p=0.019). 95% confidence intervals are depicted with dotted lines.

Abbreviations: ACC= anterior cingulate cortex; RCFT= Rey-Osterreith Complex Figure Test; TMT-A= Trail Making Test, part A.

DISCUSSION

This study demonstrated that each sub-region of the ACC had distinctive rs-FCNs in the OCD group, in which the strengths of the functional connectivity between ACC seeds versus specific components of the CSTC loop were altered. Our results also showed that altered rs-FC strength between the CSTC loop components and the ACC sub-regions was associated with executive dysfunction in OCD.

The CSTC loop model of OCD (71) proposes the involvement of direct and indirect cortico-striato-thalamic pathways, in which imbalances between these frontal–striatal circuits may mediate OCD symptomatology. The direct pathway is composed of the ventromedial frontal (ventral ACC and OFC)–ventral striatal (internal part of the globus pallidus) circuit, which results in thalamus disinhibition and thus an increased excitatory effect on the prefrontal cortex. In contrast, the indirect pathway is associated with a dorsal frontal (DLPFC and dorsal ACC)–dorsal striatal circuit and provides a mechanism of negative feedback, which is important for inhibition and switching of behavior. In this study, five seeds of the ACC, a central component of the CSTC loops in patients with OCD, constructed distinct patterns of rs-FCNs, in agreement with previous results in healthy subjects (69). However, between-group analyses revealed reduced rs-FCN strength in the claustrum, thalamus, and IPL in patients with OCD, which could be related to OCD symptomatology and impaired cognitive functioning.

Overall, each seeds of the ACC subregions constructed distinct patterns of rs-FCNs as a whole, consistent with the previous studies for healthy subjects which showed several distinct ACC-based rs-FCNs based on the functional segregations of ACC subregions, which are the motor control (S1), cognitive control (S3), conflict monitoring (S5), social processing (S7) and emotional regulation (I9) (69). In this study, the OCD group revealed reduced rs-FC strength in the brain areas which were indeed important components of the CSTC loop, namely the claustrum and the pulvinar of the thalamus (72), and in the inferior parietal lobule. As rs-FCNs reflect ongoing information processing between relevant brain areas during the task-free status and also shows regional brain activities during task performance(37), disruption of these rs-FCN strength and pattern could be a reflection of functional derangement in the relevant brain area.

We showed decreased regional functional connectivity between the ACC S1 seed and the left claustrum and between the ACC S5 seed and the right claustrum in the OCD group. The supragenual ACC, which includes the S5 seed, is typically associated with evaluative functions of reasoning (73), conflict detection (74, 75), and response to error (75). The claustrum, thin layers of gray matter tissue that reside between the insula and putamen, may receive, channel, and relay sensory information between several brain areas, namely many other neocortical areas in the frontal (76), temporal (77), and parietal cortices (78), as well as limbic structures such as the hippocampus (79), amygdala (80), caudate nucleus and putamen (81), comprising neural circuits subserving cognitive function (82) including the CSTC loops.

The RCFT task requires subjects initially to copy a complex geometric figure and then to reproduce that same figure based on the memory during the immediate and the delayed recall phase. As reproduction of that complex figure could be conducted only by the usage of organization strategies of frontal lobe functioning, the RCFT has been used as a valuable measure of executive functioning (12). In this study, we found no statistically significant differences in RCFT organization score between the patients with OCD and the healthy controls (p = 0.510), which is in line with our previous studies (53, 83). However, stronger regional functional connectivity between the S5 ACC seed and the right claustrum successfully predicted a higher RCFT organization score only in patients with OCD, raising the possibility that degrees of functional coherence between the supragenual ACC and the claustrum may be the neural correlate of the visual organization strategy in patients with OCD.

The subgenual ACC, which included Seed I9, is the central component of the limbic and paralimbic system, composed of the amygdala, insula, ventral striatum, and ventral regions of the ACC (84), subserves emotional responsiveness and regulation and the monitoring of rewarding or punishing outcomes (85). The subgenual ACC is involved in identifying the emotional significance of a stimulus and producing a relevant affective state as a response. The OFC is involved in the evaluation of motivational significance, generation of adaptive responses to rewarding or aversive stimuli, and regulation of emotional states. As a result, hyperactivity of OFC could disrupt the evaluative function for the consequences of immediate action, resulting in uncontrolled thoughts and behaviors (86). Considering these observations, an exceptionally strengthened rs-FC between the ACC I9 seed and OFC in the OCD group, which was revealed in this study, may be related to the strong anxiety precipitated by overvalued ideas regarding one's behaviors and thoughts.

This study showed that the weaker functional connectivity between the perigenual ACC S7 seed and the right IPL was significantly correlated with longer reaction times for completing the TMT-A task. Perigenual ACC, which includes the S7 ACC seed, has repeatedly been implicated in social cognitive functions, such as mentalizing (theory-of-mind) (87, 88) and self-reflection (89, 90). The IPL is a component of the so-called fronto-parietal control network, which consists of the DLPFC, ACC, and IPL, regulating cognitive control and decision-making processes (91). In this fronto-parietal control network, the IPL mainly supports proper task execution by taking part in motor response preparation and visuospatial processing (92). Especially, the right IPL has been linked to the function of visuospatial memory, including the ability to sense relationships between body parts. It is also related to the perception of our own affects or feelings. In OCD patients, time-consuming repetitive compulsive acts and preoccupations to specific body parts or somatic discomforts could be related to the impaired self-reflection which underlies the functional impairment of the fronto-parietal control system. Some case reports have stressed the temporal relationships between OCD symptomatology and brain hemorrhage (93) and multiple sclerosis plaques (94) of the right parietal lobe. Similarly, disrupted structural connectivity (95) and altered chemical composition of white matter (96) in the supramaginal gyrus of the IPL subdivisions, have been linked to several executive dysfunctions including visuospatial ability and nonverbal memory as well as OCD symptom severity (97). Accordingly, defects in striato-fronto-parietal connectivity may underlie the inefficient information processing in OCD (98), which results in slowed psychomotor speed.

Relatively attenuated strength of rs-FC anti-correlation between ACC seeds and posterior brain areas should also be mentioned, as insufficient deactivation of specific brain areas in relation to ACC activation could result in inefficient information processing and impaired execution. Previous structural and functional neuroimaging studies revealed significantly lowered FA of lingual gyrus(95), excessive BOLD response of parahippocampal gyrus in decision of whether to discard personal items or not(99) and increased BOLD response in response to biological motion stimuli(100), which were in line with our study results.

There are some more issues to be discussed. This study did not consider OCD subtypes in the rs-FCN analyses. However, if we accept the concept of OCD as one disease entity with common pathophysiology encompassing several symptom subtypes, rs-FC may reflect this common pathophysiology successfully. We also did not investigate rs-FCNs regarding left ACC seeds because previous studies of rs-FC for the ACC regions showed hemispheric similarity for the patterns of ACC connectivity (43, 101).

Our results, obtained from well-developed methodology, showed the importance of the ACC as a central executor in the CSTC loops of OCD (43). Using the rs-FCN approach, the patterns of which resemble the topographic activation patterns of the same regions during task performance (102), we provided evidence that the regional functional connectivity between ACC subregions and some components comprising the CSTC loops may be the neural correlates of executive dysfunction in OCD. Additionally, we revealed some beneficial clues pointing to the parietal cortex, particularly the IPL, as one of the important brain regions included in the OCD pathophysiology loops. Future research for causal relationships between brain regions related to the ACC rs-FC is needed.

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국문 초록

서론: 앞쪽 띠피질은 강박증의 유력한 신경해부학적 가설인 피질-피질하 신경회로 이상 모델을 구성하는 중요한 뇌부위로서, 강박증 환자에서 앞쪽 띠피질의 기능 이상은 강박 증상 및 실행기능의 손상과도 관련되어 있을 가능성이 제기되어 왔다. 본 연구에서는 운동기능 조절, 주의력 통제, 상반된 정보들을 바탕으로 한 의사결정 및 감정조절 등 각각의 수행 기능에 따라 앞쪽 띠피질을 다섯 개의 세부 영역으로 나눈 후, 이러한 세부 영역 각 부위들과 다른 뇌 부위들 사이의 휴지기 기능적 뇌연결성을 관찰하고 정상인의 경우와 비교한 후, 강박증 환자에서 앞쪽 띠피질과 다른 뇌부위들 사이의 휴지기 기능적 뇌연결성의 변화가 다양한 실행기능의 손상 사이의 관계를 규명하고자 하였다.

방법: 본 연구에서는 이전에 정신과 약물 투약력이 없거나 혹은 연구 참여 당시로부터 최근 4주 이상의 기간 동안 정신과 약물을 투약하지 않은 21명의 강박증 환자와 22명의 정상 대조군을 대상으로 하여, 특정한 과제를 수행하지 않는 휴식 상태에서 기능적 뇌 자기공명영상을 촬영하였다. 이와 같이 얻어진 영상을 이용하여, 앞쪽 띠피질의 전장에 걸쳐 균일한 간격으로 분포된 관심 영역 중, 이전의 기능적 뇌영상 연구를 통해 앞쪽 띠피질이 수행하는 다양한 실행기능과의 관련성이 시사되는 다섯 개의 관심 영역을 선정하고, 이들 관심 영역들 각각과 이외의 다른 뇌 영역들 사이에 구성되는 휴지기 기능적 뇌연결성의 양상을 탐색하였다. 더불어, 강박증 환자군과 정상 대조군 사이에서 휴지기 기능적 뇌연결성의 강도가 유의한 차이를 보이는 경우, 앞쪽

띠피질의 관심영역과 해당 뇌영역 사이 기능적 연결성의 강도와 실행기능 손상 정도 사이의 관련성을 검증하였다.

결과: 강박증 환자와 정상 대조군 모두에서, 앞쪽 띠피질의 문측으로부터 미측까지 분포하는 다섯 개의 관심영역들은 각기 서로 다른 형태의 휴지기 기능적 뇌연결성을 보이는 공통점이 있었다. 두 군을 비교하였을 때, 정상 대조군에 비해 강박증 환자군은 앞쪽 띠피질과 시상, 하측 두정엽 및 담장(claustrum)과의 휴지기 기능적 뇌연결성이 유의하게 감소되어 있었다. 이 중 앞쪽 띠피질의 무릎 위쪽 부위에 위치한 S5 관심영역과 담장 사이의 기능적 연결성이 강할수록 레이 복합도형검사의 구조화 점수가 우수하였고, 앞쪽 띠피질의 무릎 밑쪽 부위에 위치한 S7 관심영역과 우반구의 하측 두정엽 사이의 기능적 연결성이 강할수록 길 만들기 검사 A형 수행시의 수행시간이 짧아지는 양상이 관찰되었다.

결론: 본 연구의 결과는 강박증의 피질-피질하 신경모델을 구성하는 앞쪽 띠피질과 다른 뇌 영역들 사이의 휴지기 기능적 뇌연결성 변화가 강박증에서의 실행기능 손상과 관련되어 있음을 보여 준다. 또한 전전두엽의 영역들뿐만 아니라 하측 두정엽 또한 강박증의 피질-피질하 신경모델에서 정보처리 속도 등과 관련하여 중요한 구성 요소로 작용할 가능성을 시사한다.

주요어: 앞쪽 띠피질, 휴지기 기능적 뇌연결성, 기능적 뇌 자기공명영상, 강박증, 집행기능

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